Remarks

The Office Action mailed December 18, 2002 has been received and reviewed. Claims 11-7, 11, 19-21 and 23-25 are identified as pending in the Office Action. Applicants note that by the preliminary amendment filed with the application on October 27, 2000, claims 2, 4, 7 11 and 21 were canceled and additional claim amendments were made, thus claims 1, 3, 5, 6, 19, 20 and 23-25 are currently pending. Should the Office request a replacement copy of the Preliminary Amendment, applicants will gladly provide one. Claims 2-4, 7, 11, 21 and 23 were noted as withdrawn from consideration in the Office Action, claims 2, 4, 7, 11 and 21 were earlier canceled rendering this withdrawal moot as to them. Applicants thus note that claims 3 and 23 are withdrawn from consideration. Claims 1, 5, 6, 19, 20, 24 and 25 stand rejected in the Office Action. Applicants have amended claims 1, 6, 19 and 20. Reconsideration of the claims as amended is respectfully requested.

Specification Objections

The Office Action requested that a number of amendments to the specification be made, including spelling out the term "TTRAP" at page 2, line 12, the term "TNF" at page 2, line 17, the term "GVHD" at page 17, line 16 and the term "GST-CD40" at page 25, line 26. It was also requested the phrase "SEQ ID NO." be corrected to "SEQ ID NO:" throughout the specification. Applicants have entered these changes by this amendment and respectfully submit no further action is required on these points.

Rejection of claims under 35 U.S.C. § 112

Rejection of claims 1, 5, 6, 19-20 and 24-25 under 35 U.S.C. § 112, 2nd ¶

Claims 1, 5, 6, 19-20 and 24-25 were rejected in the Office Action as assertedly indefinite under the second paragraph of 35 U.S.C. § 112. Applicants respectfully submit that, as amended, the claims are definite and request they be allowed.

Claim 1 was rejected as assertedly indefinite with respect to the term "capable of". The Office Action further asserted that claim 1 was vague with respect to the term "depicted in SEQ ID NO: 2." The

Office Action further required the term "TNF" be spelled out in its first recitation of claim 1, and that a comma preceding thee term "including" be removed. Applicants have accordingly amended claim 1 to remove the term 'capable of' along the lines suggested in the Office Action, to remove the term "depicted in" as suggested by the Office Action, to spell out tumor necrosis factor ("TNF") and to remove the noted comma. Applicants respectfully submit that amended claim 1 is definite and request it be allowed.

Claim 6 was noted in the Office Action as awkward in recitation with respect to the phrase "protein claim 1". Accordingly, it has been amended to recite "protein of claim 1" and applicants respectfully submit no further action is required on this point.

Claim 19 was asserted to be unclear in the Office Action with respect to the language "one or more isolated functional proteins" and to be indefinite with respect to the language "and/or". Applicants have amended claim 19 to address these issues and respectfully submit that claim 19 is definite and request it be allowed.

Claim 20 was asserted to be indefinite in the Office Action with respect to the language "the CD40 related pathway". Applicants have amended claim 20 as suggested in the Office Action ad respectfully submit amended claim 20 is definite and request it be allowed.

Rejection of claims 1, 5, 6, 19 and 20 under 35 U.S.C. § 112, 1st ¶

Claims 1, 5, 6, 19 and 20 were rejected in the Office Action as assertedly lacking enablement under the first paragraph of 35 U.S.C. § 112. Applicants respectfully traverse this rejection and submit that, as amended, claims 1, 5, 6, 19 and 20 are enabled. The Office Action states:

> "the specification, while being enabling for isolating CD40 interacting protein, *i.e.*, TTRAP (TRAF and TNF receptor associated protein) SEQ ID NO:2, identifying TTRAP interactions with TNF (tumor necrosis factor) receptor, TRAF (TNF receptor-associated factor), and CD40 protein, does not reasonably provide enablement for all polypeptide variants having 70-100% homology to or a fragment of SEQ ID NO:2, and a pharmaceutical composition comprising a compound interacting with the polypeptide variants for treating a CD40-related disease." (Office Action at page 5).

A number of factors are set forth in MPEP § 2164.01(a) to be considered in determining whether any experimentation that is required to practice an invention would be undue. The MPEP states that "analysis must consider all evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole." Applicants note that one important factor "(F) The amount of direction provided by the inventor" was not discussed in the Office Action. Applicants respectfully submit that consideration of all the *Wands* factors makes it clear that the claims, as amended, are enabled.

The first factor discussed in the Office Action is the "nature of the invention" (*Office Action* at page 6). The Office Action states that the 'current disclosure provides no working examples with respect to structure and function of these variants nor how to *a priori* determine which ones(s) would or would not have been functional." The Office Action then concludes there "is insufficient guidance as to which amino acid residue within the polypeptide can be deleted, substituted...." and further states the "application discloses only the cDNA-encoded SEQ ID NO:2." Applicants respectfully traverse these conclusions.

The present application discloses a 362 amino acid protein (SEQ ID NO:2) which strongly bonds to CD40, CD30, and TNFRII, among other receptors of the super family (*see* Table 1). In addition, the present application also discloses a murine homologue of 371 amino acids (SEQ ID NO:4) with amino acids that are 70% similar to SEQ ID NO:2 (*see* page 4 of the specification), and a possible TTRAP homologue from *C. elegans* which is 30% identical to TTRAP (*see,* Example 8 on pages 23-24 of the specification).

Further, the present application identifies which of the amino acids of TTRAP are important for binding the TNF superfamily receptors. An indication that amino acids 274-362 are important for binding can be obtained from Table 1 and pages 3-4 of the application, and amino acids 115-121, 145-153 and 347-352 are indicated as important for binding at the paragraph beginning at page 4, line 18 of the application. Since the application identifies which amino acids are important, indicating which should be conserved, and identifies a number of related proteins, applicants submit this factor supports a conclusion that the amended claims are enabled and request they be allowed.

The second factor discussed in the Office Action is the "scope of the claims" (*Office Action* at page 8). The Office Action discusses this factor with respect to only independent claim 20 and states "the term 'interacting' in the claims encompasses positive or/and negative regulation". Applicants note that the Office Action rejected the language "capable of interacting" as indefinite in claim 1. Accordingly, claim 1 has been amended to remove this language as suggested in the Office Action. Applicants submit that, as amended, the scope of claim 1, with the claims dependent therefrom, is supported by the enabling disclosure and this rejection should be withdrawn and such claims allowed. Further, with respect to independent claim 20, applicants note that independent clam 20 is only discussed in the Office Action in connection with this single *Wands* factor and that all other *Wands* factors, as discussed herein, support the allowability of all claims. As set forth in MPEP 2164.01(a) a single *Wands* factor cannot form a basis for a determination of nonenablement. Accordingly, applicants request this rejection be withdrawn and amended claim 20 be allowed.

In examining the "state of the prior art", the Office Action states "the disclosure fails to describe common attributes and characteristics that identify any biological active fragments for its use, one of skilled artisan is require performing undue experimentation in order to screen, identify and isolate appropriate truncated full-length TTRAP polypeptides." (*Office Action* at page 9). As discussed previously herein, the present specification discloses a number of homologous polypeptides and identifies amino acids of TTRAP that are important for binding (common attributes and characteristics). Applicants thus respectfully submit the analysis in the Office Action, in light of these additional facts, supports a conclusion of enablement.

Similarly, with respect to the "unpredictability of the art" and "quantity of experimentation necessary" factors discussed in the Office Action at pages 9-10, consideration of these additional facts and the claim amendments make it clear that such factors support a conclusion of enablement.

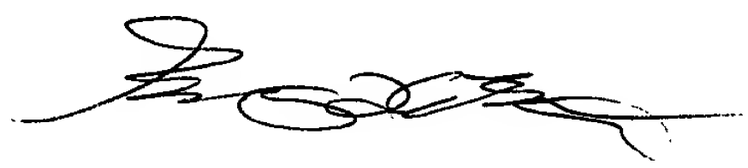
In conclusion, applicants respectfully submit that the structural information regarding which amino acid residues important for binding, and the disclosure of multiple polypeptide homologues of TTRAP, provide guidance that enable a person of ordinary skill on the art to determine which variant or fragment

of TTRAP shall most probably "form a complex with receptors of the TNF superfamily". Accordingly, applicants respectfully submit that as amended claims 1, 5, 6, 19 and 20 are enabled and request they be allowed.

CONCLUSION

All pending claims are believed to be in condition for allowance, and an early notice thereof is respectfully solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Examiner is respectfully invited to contact Applicants' undersigned attorney.

Respectfully submitted,



Bretton L. Crockett
Registration No. 44,632
Attorney for Applicants
TRASKBRITT, PC
P. O. Box 2550
Salt Lake City, Utah 84110-2550
Telephone: (801) 532-1922

Date: March 18, 2003

MARKED UP VERSION SHOWING CHANGES MADE

IN THE SPECIFICATION:

Please amend the paragraph beginning at page 2, line 7 to read as follows:

[Technical Field] **Technical Field**: The invention relates to CD40 binding proteins, which can be used as modulators of the CD40 signaling pathway and/or the CD40-induced nuclear factor kappa B (NF-κB) activating pathway and thus useful in the treatment of CD40 related diseases (*e.g.*, inflammatory diseases) and/or NF-kB related diseases and/or in the improvement of anti-tumor treatments. The current invention also relates to nucleic acid sequences coding for the CD40 interacting proteins (also called "TTRAP" ("TRAF and TNF receptor associated protein") for CD40 receptor associated protein). The invention further relates to the use of the polypeptides derived from these CD40 interacting proteins in the treatment of CD40 and/or NF-kB related diseases and/or cancer. Furthermore, the invention concerns pharmaceutical preparations comprising the CD40 interacting proteins or polypeptides derived from these proteins.

Please amend the paragraph beginning at page 2, line 17 to read as follows:

[Background] **Background**: CD40 is a receptor of the tumor necrosis factor ("TNF") - receptor superfamily (Banchereau *et al.*, 1994), which is expressed at the surface of B-cells, antigen presenting cells (APC), and several non-hematopoietic cells such as endothelial cells (Hollenbaugh *et al.*, 1995), epithelial cells (Galy & Spits, 1992), fibroblasts (Fries *et al.,* 1995) and keratinocytes (Gaspari *et al.*, 1996). The ligand for CD40 (CD40L) occurs mainly on activated T-cells. Up to now the role of CD40 was mainly studied in the context of the T-cell APC / B-cell interaction (for a review, see Noelle, 1996). Amongst others, the CD40-CD40L interaction seems to be important for the T-cell mediated immunity and for primary and secondary humoral immune response. These findings were confirmed by experiments in mouse models showing that treatment with anti-CD40L antibodies resulted in blocking of the development of mouse equivalents of human autoimmune diseases such as arthritis (Durie *et al.* 1993) , oophoritis (Griggs *et al.,* 1996) and multiple sclerosis (Gerritse *et al.,* 1996).

Please amend the paragraph beginning at page 4, line 8 to read as follows:

The invention also includes an isolated functional protein either comprising an amino acid sequence with 70-100% homology to the amino acid sequence depicted in SEQ ID NO[.] : 2 or either comprising an amino acid sequence with 70-100% homology to the amino acid sequence depicted in SEQ ID NO [.] : 4 or in the alternative comprising an amino acid sequence with 70-100% homology to the amino acid sequence depicted in SEQ ID NO[.] : 6.

Please amend the paragraph beginning at page 4, line 13 to read as follows:

More specifically, the functional protein comprises an amino acid sequence with 70-100% homology to the amino acids 54-362 of SEQ ID NO [.] : 2, even more specifically the functional protein comprises an amino acid sequence with 70-100% homology to the amino acids 274-362 of SEQ ID NO [.] : 2 or in the alternative and/or comprising an amino acid sequence with 70-100% homology to the amino acids 2-245 of SEQ ID NO [.] : 6.

Please amend the paragraph beginning at page 4, line 18 to read as follows:

Furthermore, the invention also includes those proteins or peptides having 70-100% homology to, at least, any of the three peptides as depicted in SEQ ID NO [.] : 2 located between the residues 115-121, 145-153 and 347-352 respectively. The amino acid sequence of residue numbering 115-121 is SLITWNI; the amino acid sequence of residue numbering 145-153 is PDVIFLQEV and the amino acid sequence of residue numbering 347-352 is FPSDHW.

Please amend the paragraph beginning at page 5, line 17 to read as follows:

One embodiment of the invention is a protein with SEQ ID NO [.] : 2. Another embodiment of the invention is a protein with SEQ ID NO [.] : 4. A further embodiment of the invention concerns a protein with SEQ ID NO [.] : 6.

Please amend the paragraph beginning at page 7, line 16 to read as follows:

Another aspect of the invention involves DNA molecules, also called nucleic acid sequences, encoding for the aforementioned proteins, preferably a nucleic acid sequence with 70-100% homology to the DNA sequence depicted in SEQ ID NO [.] : 1 and/or a nucleic acid sequence with 70-100% homology to the DNA sequence depicted in SEQ ID NO [.] : 3 or in the alternative a nucleic acid sequence with 70-100% homology to the DNA sequence depicted in SEQ ID NO [.] : 5.

Please amend the paragraph beginning at page 16, line 8 to read as follows:

"Compound" means any chemical or biological compound, including simple or complex inorganic or organic molecules, peptides, peptido-mimetics, proteins, antibodies, carbohydrates or nucleic acids, that interferes with the interaction of a protein depicted in SEQ ID NO [.] : 2, SEQ ID NO: 4, or SEQ ID NO: 6 with a compound of the CD40 and/or NF-kB related pathway.

Please amend the paragraph beginning at page 16, line 25 to read as follows:

The functional protein of the invention is administered at a concentration that is therapeutically effective to prevent allograft rejection, graft versus host disease (" GVHD ") , allergy and autoimmune diseases. The dosage and mode of administration will depend on the individual. Generally, the compositions are administered so that the functional protein is given at a dose between 1 mg/kg and 10 mg/kg, more preferably between 10 mg/kg and 5 mg/kg, most preferably between 0.1 and 2 mg/kg. Preferably, it is given as a bolus dose. Continuous short time infusion (during 30 minutes) may also be used. The compositions comprising the functional protein according to the invention may be infused at a dose between 5 and 20 mg/kg/minute, more preferably between 7 and 15 mg/kg/minute.

Please amend the paragraph beginning at page 17, line 10 to read as follows:

With regard to the use of the functional protein of the present invention to prevent allograft rejection, it should be stressed that the proteins of the present invention or the compositions comprising the

same may be administered before, during or after the organ transplantation as is desired from case to case. In case the protein or the compositions comprising the same are administered directly to the host, treatment will preferably start at the time of the transplantation and continue afterwards in order to prevent the activation and differentiation of host T cells against the major histocompatibility complex ("MHC") on the allograft. In case the donor organ is *ex vivo* perfused with the functional protein according to the invention or the compositions comprising the same, treatment of the donor organ ex vivo will start before the time of the transplantation of the donor organ in order to prevent the activation and differentiation of host T cells against the MHC on the allograft

Please amend the paragraph beginning at page 19, line 2 to read as follows:

Full length human TTRAP cDNA was obtained by screening a HUVEC cDNA library with the TTRAP fragment as probe. A cDNA of about 2 kb was isolated, with an open reading frame of 1086 nucleotides encoding for a protein of 362 amino acids (SEQ ID NO [.] : 2).

Please amend the paragraph beginning at page 19, line 5 to read as follows:

The mouse TTRAP homologue was obtained by screening the EST database and aligning the homologous sequences. Human and mouse TTRAP are approximately 65% identical and 70% similar on the amino acid level. The mouse sequence is shown in SEQ ID NO [.] : 3.

Please amend the paragraph beginning at page 19, line 9 to read as follows:

Nucleotide sequence analysis was carried out using dye terminator mix and a 310 Genetic analyzer from Perkin Elmer. The nucleotide sequence of TTRAP is shown in SEQ ID NO [.] :1 whereas the sequence of 4C4 is shown in SEQ ID NO [.] : 5.

Please amend the paragraph beginning at page 21, line 13 to read as follows:

4C4 protein is interacting with CD40, CD30, TNF-RII, with the longest fragment of TTRAP and with a deletion mutant of TRAF3 which still contains the largest part of the TRAF domain (from aa 380 to the carboxy terminal end of the protein. A smaller form of 4C4 (from amino acid 2 - amino acid 245 in SEQ ID NO [.] : 6) is also capable to interact with CD40.

Please amend the paragraph beginning at page 25, line 20 to read as follows:

Fas and CD40 are both members of the TNF-Receptor superfamily. DAXX was originally isolated as a Fas-binding protein, in a yeast two-hybrid screen (Yang et al., Cell, 89, 1067-76, 1997). The protein was shown to interact specifically with the death domain of Fas. It was reported to play a role in apoptosis via the activation of the Jun N-terminal kinase. The authors examined the binding of a partial clone of human DAXX (from amino acid 501 till the end) to the cytoplasmic tail of mouse CD40, and could not detect interaction. In addition, an *in vitro* interaction assay of full length DAXX with glutothione S-tranferase-CD40 ("GST-CD40") also turned out to be negative. Therefore, the authors conclude that DAXX does not associate with CD40.

IN THE CLAIMS:

Please amend the claims as follows:

1. (Three Times Amended) An isolated protein [capable of interacting] characterized by an ability to form a complex with receptors of the Tumor Necrosis Factor ("TNF") superfamily including the cytoplasmic domain of CD40, said isolated protein comprising an amino acid sequence having 70-100% homology to the amino acid sequence [depicted in] of SEQ ID NO: 2 or a fragment thereof [capable of interacting] said isolated protein characterized by an ability to form a complex with receptors of the TNF superfamily [,] including the cytoplasmic domain of CD40.

6. (Three Times Amended) The isolated protein of claim 1 wherein said isolated protein is a fragment comprising the amino acids 274-362 of SEQ ID NO: 2.

19. (Two Times Amended) A pharmaceutical composition comprising [one or more] the isolated functional [proteins] protein of claim 1 [and/] or functional fragments thereof and a pharmaceutical acceptable carrier material. [.]

20. (Two Times Amended) A pharmaceutical composition for treating a CD40-related disease, said pharmaceutical composition comprising:

at least one compound produced by interacting the isolated protein of claim 1 [and/] or said fragment thereof with other protein components of the CD40 [related] mediated signaling pathway, and detecting the at least one compound's effect on said interaction; and

a pharmaceutical acceptable carrier material.